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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/019,816	03/27/2002	Michael Valentine Agrez	SW-046 XX	9944

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EXAMINER	
CANELLA, KAREN A	
ART UNIT	**PAPER NUMBER**
1643	

DATE MAILED: 11/21/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/019,816	AGREZ ET AL.	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *17-219,221,225,238,244,245,266-269,272 and 275-282* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *17-219, 221, 225, 238, 244, 245, 266, 267, 268, 269, 272 and 275-282* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim 220, 242, 243, 247, 249, 252-254, 264, 265, 270, 271, 273, 274 have been canceled. Claims 217, 218, 219, 221, 244, 245, 266, 267, 268, 269 have been amended. Claims 275-282 have been added. Claims 217-219, 221, 225, 238, 244, 245, 266, 267, 268, 269, 272 and 275-282 are pending and under consideration.

Sections of Title 35, U.S. Code not found in this action, can be found in a prior action.

It is noted that support for the binding of Beta6 to ERK2 or JNK-1 can be found on pages 28-33; support for the binding of ERK2 to beta3 and beta5 can be found on page 34, lines 4-5.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 217-219, 221, 225, 238, 244, , 245, 266, 267, 268, 269, 272 and 275-282 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 217 and 266 recite "wherein the binding domain of the β integrin subunit". It is unclear if the β integrin subunit referred to in the following clause pertains only to the polypeptide having the modified amino acid sequence, or if it is to be applied to the polypeptide comprising the cytoplasmic fragment of a β integrin subunit. Claims 217 and 266 recite "modified amino acid sequence compared to the binding domain". It is unclear what binding domain this is in reference to. Claims 217 and 266 recite "amino acid linker sequence which link opposite end regions of the binding domain together and which is non-essential for the binding of MAP kinase. It is unclear if the linker is non-essential for the binding o MAP kinase or the end regions of the binding domain. Claims 217 and 266 recite "50% overall sequence homology with the binding domain". It is unclear what binding domain this is in reference to. Claims 217 and 266 recite "sufficient amino acid sequence homology with both the end regions of the binding domain to bind to the MAP kinase". This is unclear because of the statement that the

"opposite ends of the binding domain" are non-essential for the binding to MAP kinase above. The recitation of "the β integrin subunit expressed by the cancer cell" is vague and indefinite because such expression has no antecedent basis within the claim, and further it is unclear if this limitation is to be applied to the method wherein the polypeptide having the modified amino acid sequence is used for treating the cancer cell, or if it is to be applied to the treatment of the cancer cell with polypeptide comprising the cytoplasmic fragment of a β integrin subunit.

It is unclear how claim 268 further limits claims 266 and 267 Claims 266 and 267 require the polypeptide comprising the modified amino acid sequence have a amino acid linker sequence. Claim 268 requires that one or more amino acids in the amino acid linker sequence have been deleted. It is unclear how the deletion of an amino acid in a linker sequence further modifies the scope of claims 267 and 266 because claims 267 and 266 encompass linker sequences of various lengths, and the hypothetical deletion of an amino acid sequence is not clear unless the sequence is set forth in claims 267 and 266 because "deletion" can only be measured relative to the parent amino acid sequence. Further claim 268 encompasses "one or more" amino acids which reads on the deletion of the entire linker sequence, as exemplified by claim 279, said linker sequence being required for the modified polypeptides of claims 267 and 266.

It is unclear how claim 245 and 275 further limit claim 217. Claim 217 requires that the polypeptide comprising the modified amino acid sequence have an amino acid linker sequence. Claim 245 requires that one or more amino acids in the amino acid linker have been deleted. It is unclear how the deletion of an amino acid in a linker sequence further modifies the scope of claim 217 because claim 217 encompasses linker sequences of various lengths, and the hypothetical deletion of an amino acid sequence is not clear unless the sequence is set forth in claim 217 because "deletion" can only be measured relative to the parent amino acid sequence. Further claim 245 encompasses "one or more" amino acids which reads on the deletion of the entire linker sequence, as exemplified by claim 275, said linker sequence being required for the modified polypeptides of claim 217.

Claims 276 and 280 are vague and indefinite in the defining of the end regions of the binding domain as a function of sequences which are unchanged in the modified amino acid

sequence as compared to the binding domain because claims 245 and 268 require that the end regions are manipulated by means of a linker sequence to form a modified amino acid sequence. this does not serve to define the ends of the binding domain because the amino acid linker sequence links both ends of the domain, and therefore the domain has been manipulated and is changed and cannot fulfill the limitation of being unchanged.

Claims 217-219, 221, 225, 238, 244, , 245, 266, 267, 268, 269, 272 and 275-282 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of inhibiting the growth of a cancer cell ex vivo or in vitro comprising contacting said cell with a polypeptide fragment of the domain of beta6, 3 or 5, responsible for the direct interaction with ERK2, or contacting the polypeptide fragment of the domain of beta6 responsible for the direct interaction with JNK-1, does not reasonably provide enablement for the disruption of the binding of ERK2 or JNK1 to any other beta integrin subunit, or the disruption of the binding of any other ERK or JNK MAP kinase to the genus of beta integrins by "agents" other than the aforesaid fragments of the cytoplasmic domain of beta3, beta5 or beta6 or the peptides of SEQ ID NO:2, 2, 22 and 23, or the inhibition or prophylaxis of cancer within a patient. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims..

(A) as drawn to the prophylaxis of cancer

claim 266 now requires that the method be intended for patients believed to be at risk o suffering from cancer. when given the broadest reasonable interpretation, the claim encompasses the prevention of cancer in said patients believed to be "at risk", such that . In order to carry out the claimed method for prevention, it would be necessary to know which individuals are at risk for developing cancer, the location of said cancer, the time at which the cancer would develop and the length of time before said development of the cancer at which the instant methods should commence. The specification fails to address any of these issues, thus one of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to ;practice the claimed methods on patients believed to be at risk from suffering from cancer.

Applicant argues that the deletion of the term prophylaxis rendered moot the rejection. this is not persuasive because treating a patient "at risk" for suffering from cancer is tantamount to preventing the onset of cancer in said patient.

(B) As drawn to the administration of polypeptides in vivo

Further, the claims encompass a method of treating an individual having a cancer comprising administering polypeptide sequences. The art recognizes general problems with the administration of protein drugs, namely short half-life in vivo, necessitating multiple administrations (Johnson and Tracey, 'Peptide and Protein Drug Delivery', In: Encyclopedia of Controlled Drug Delivery, Vol. 2, 1999, pages 816-833). The art teaches that "major stability, release and manufacturing challenges" (page 816, second column, lines 1-5) must be met in order to overcome the technical difficulties associated with the delivery of proteins in vivo. The specification does not teach a means for the delivery of the polypeptide agents to the appropriate site and the efficacious uptake by the tumor to result in the inhibition of cancer cells in a patient. Therefore it would be undue experimentation in order for one of skill in the art to determine the required dosage for the required length of time, and the means to stabilize and then release said polypeptides in vivo using techniques which preserve the ability of said polypeptides to function as claimed.

Applicant argues that the specification is enabling for the administration in vivo by use of facilitator moieties on pages such as carrier peptides. This has been considered but not found persuasive. The carrier peptides such as penetratin, described in the specification are not specific; they will not function to target the tumor cells. further, the fate of the plasma membrane transported cargo is unclear. There is no objective evidence in the specification that attachment of the carrier peptide will provide the polypeptide or modified polypeptides of the instant invention to the location of the cell where MAP kinase is present. The art provides evidence that penetratin/antennapedia is designed to migrate to the nucleus (Perez et al, journal of Cell Science, 1992, pp. 717-722). The specification provides no teaches as to how an attached peptide can remain in the cytoplasm when attached to such a carrier peptide, nor does the peptide

teach that the interaction of the modified polypeptide with JNK MAP kinase is possible under the expected conditions of transport through the cytoplasm.

(C)As drawn to the direct interaction between the JNK or ERK MAP kinase families and integrin beta subunits

The claims are broadly drawn to methods which encompass the binding of any cytoplasmic fragment of a integrin beta subunit with any MAP kinase. Applicants amendment specifying that the cancer cell selected from the group consisting of β3, β5 or β6 fails to modify the selection of a polypeptide comprising a cytoplasmic fragment of a β integrin subunit of the administered polypeptide It is noted that the priority document filed 28 June 1999 states that although no MAP kinase or any other subunit form of MAP kinase has been shown to bind to any of the 23 known integrins, the inventors have surprising determined that MAP kinase binds directly to the cytoplasmic domain of alpha-v-beta6 (page 2, lines 14-17). It is further noted that applicant has amended the claims to delete the requirement that the MAP kinase is ERK or JNK MAP kinase and thus the claims encompass methods requiring the interaction between broadly claimed MAP kinases and domains taken from integrin beta subunits. Thus it would be undue experimentation, without reasonable expectation of success to practice the broadly claimed methods which encompass any integrin beta subunit, because the prior document actually teaches away from using the method directed to the interaction between ERK2 and the beta subunits which are not beta3, 5 and 6 subunits, or the interaction with JNK-1 with beta subunits which are not beta6. The art recognizes that MAP kinases comprising three different families: the ERK, JNK and p38, and that individual members participate in different signaling cascades (Garington and Johnson, Current Opinion in Cell Biology, 1999, Vol. 11, pp. 211-218, reference of the IDS filed July 30, 2002, page 212, figure 1) and are regulated by different scaffolding proteins (ibid, page 213, figure 2). Because MAP kinases such as ERK3-5 and p38 are present in entirely different signaling cascades and are bound by different scaffolding proteins such as MP-1 which binds to ERK1 and JIP-1 or MEKK1 both of which lead to enhanced JNK activation, one of skill in the art would reasonably conclude that the binding of ERK1 or JNK directly to the cytoplasmic domain of beta6 did not provide a nexus for the binding of any MAP kinase directly to beta6 or any other integrin beta subunit because the MAP kinases differ in protein-protein interactions with other known members in signaling cascades as exemplified by figure 2 of

Garington and Johnson. Given the lack of objective evidence in the specification for the direct binding MAP kinases which were not ERK2 or JNK-1 to an integrin beta subunit which was beta6 or any other integrin, one of skill in the art would be subject to undue experimentation in order to practice the broadly claimed method

(D)As drawn to modified polypeptides .

Claims 217, 218, 219, 221, 225, 238, 245, 266-269, 272-282 are drawn to methods reliant on the identity of a modified amino acid sequence having at least 50% overall identity with the "binding domain". The specification teaches agents which comprise the integrin-map kinase binding domain and the peptides of SEQ ID NO:2, 3, 22 and 23. The binding domain would be a function of what is being bound. In the instant case, the claims allow for binding to any MAP kinase. The specification fails to teach any structural correlation between retaining or varying the integrin binding domain sequence and the effect on the binding to any MAP kinase. Further, the art recognizes that the binding of two proteins is influences by the three dimensional conformation of each of the proteins. Variation of the primary amino acid sequence can have unforeseen consequences on a three dimensional protein structure because the art is unreliable for predicting the outcome on the three dimensional structure of a protein because the structure is government by numerous interacting forces (Ibragimova and Eade, Biophysical Journal, Oct 1999, Vol. 77, pp. 2191-2198, see page 2191, first column, lines 12-17 and second column, lines 3-8).

Given the lack of teachings in the specification regarding methods reliant on MAP kinases beyond those or EKR2 and JNK, the negative teachings of the priority document regarding the binding of JNK-1 to integrin subunits other than beta6, or the binding or ERK2 to integrin subunits other than beta3, 5 or 6, and the lack of teachings in the specification regarding the making of the required sufficiently homologous polypeptides, one of skill in the art would be subject to undue experimentation in order to practice the broadly claimed methods.

Applicant argues that the instant method requires no more than ordinary skill and it is not required of applicant to disclose all possible alternatives. this has been considered but not found persuasive for the reason set forth above. Also, the scope of the method must be commensurate with the scope of enablement set forth.

Claims 217, 218, 219, 221, 225, 238, 245, 266-269, 272-282 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 217, 218, 219, 221, 225, 238, 245, 266-269, 272-282 are drawn to in part to methods reliant on the identity of a modified amino acid sequence having at least 50% overall identity with the "binding domain", wherein said modified amino acid sequences bind to any MAP kinase.

(A) As drawn to new matter

The specification fails to provide support for the genus of modified amino acids having at least 50% identity with the binding domain. The specification contemplates that "homologues" will have 50% sequence similarity (page 25, lines 14-16), however this contemplation does not address the modified amino acid sequence comprising an amino acid linker sequence which links opposing ends of the binding domain of a β integrin subunit.

Claims 217, 266 and 268 require that an amino acid sequence link the opposing ends of the binding domain of the β integrin subunit. The specification contemplates that a polypeptide may be cyclized to provide enhanced rigidity and stability in vivo (page 47, line 16 to page 48, line 8), but this contemplation is not directed to the binding domain of the β integrin subunit or a binding domain having 50% sequence identity to a β integrin subunit, and thus fails to provide support for the instant methods.

The specification fails to provide the methods of claims 277, 278, 281 and 282 which require a range of polypeptides up to 20 amino acids in length , or from 10-15 amino acids in length.. The ranges cited on page 49 of the specification do not provide an adequate written description of the ranges claims.

(B) As drawn to inadequate written description

Thus the claims are reliant upon a genus if polypeptides which vary by 50% in sequence identity to the binding domain of a beta integrin subunit , wherein said genus of polypeptides can bind to any MAP kinase. The specification discloses the polypeptides of SEQ ID NO:2, 3, 22 and 23 which antagonize the binding to β6. The specification disclose the interaction of β3, β5

and β6 which interact with ECK and JNK MAP kinases. This disclosure fails to adequately describe the claimed genus which tolerates numerous structural deviations from the integrin β domain and binds to MAP kinases which are not ECKL nor JNK MAP kinases. One of skill in the art would reasonable conclude that applicant was not in possession of the genus of polypeptides and modified polypeptides which bind to any MAP kinase

Because the products on which a method claim is based are not adequately described, the method itself is not adequately described.

All other rejections and objections as set fort or maintained in the previous Office action are withdrawn.

All claims are rejected.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10-6:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Karen A. Canella, Ph.D.
11/12/2006

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PRIMARY EXAMINER